inflammation, in spite of suppression of the local tissue reaction, general improvement should not occur, except perhaps very fleetingly, but rather the reverse, since spread of the local infection would be facilitated.

An inquiry into the mechanism of mitosis suppression by A.C.T.H. forms one part of current investigations into the mechanism of shock by the Sheffield team. Observations on mitosis in cancer cells under similar conditions are also in progress. The changes in carbohydrate metabolism in shock and their bearing on aspects of A.C.T.H. activity, including that reported here, are being made by Stoner, Green, and Threlfall, and will, it is hoped, be published in the near future.

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DIET IN THE TREATMENT OF ACUTE HEPATITIS

BY

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It has long been thought that the diet for acute hepatitis should be rich in carbohydrates and deficient in fat. However, a number of experiments on animals (Schifrin, 1932; Goldschmidt *et al.*, 1939; Miller and Whipple, 1940; and others) showed that protein protected the liver against certain poisons such as arsphenamine and chloroform. It was further shown that the effect is principally connected with amino-acids of certain CH_3 and SH groups. Clinical investigations have been made by, among others, Darmady (1945), who treated 32 hepatitis cases with 150 g. protein and 100 g. fats, while a group of 31 cases received 70–90 g. protein and 60 g. fats. He found no difference between the two groups as regards duration of treatment, time up to normal van den Bergh reaction, or accumulation of hippuric acid. Beattie (1944) claimed that with a diet rich in protein he reduced the time of treatment by one-third. Hardwick (1945) gave 180 g. and 50 g. protein respectively, but found no difference in the results. Addition of amino-acids has also been tried (see article by J. Ström at p. 1168 of this issue).

The low-fat diet began to be abandoned a few years ago. Hoagland *et al.* (1946) treated 37 cases with 150 g. fats and 150 g. protein, while a control group of 33 cases received 50 g. fats and 150 g. protein. The only difference was that in the test series the increase in weight started earlier and was somewhat greater than in the controls. Wilson *et al.* (1946) gave 51 cases 200 g. fats and 52 control cases 70 g. fats, both groups receiving 100 g. protein. He found no difference as regards duration of treatment, bilirubinaemia, or bilirubinuria. Reich *et al.* (1947) observed no disadvantages when they included 200 g. of fats in the diet. On the other hand, a diet rich in fats has a high calorie value and is more appetizing. Fats may be given in the form of butter, milk, and cream, which contain unsaturated fatty acids: this is thought to have a certain significance, as the latter cannot be synthesized from other substances.

There are thus few clinical results available concerning diets for the treatment of acute hepatitis, and the objections to such results as have been obtained, apart from the fact that the series is a small one, are, first, that isocaloric diet has not been given, and, secondly, that there has often been a variation of more than one factor—for example, both fat and protein content.

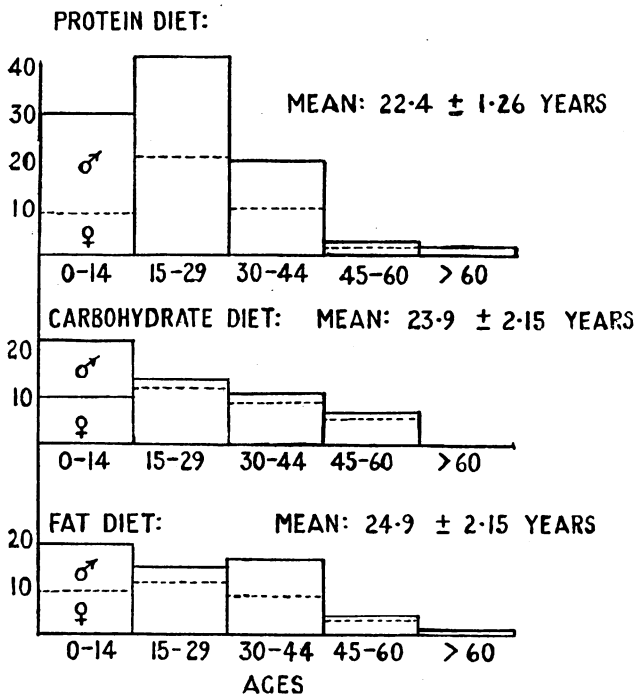
Present Investigation

Since January 1, 1949, three departments of 30–35 beds each at the Hospital for Communicable Diseases in Stockholm have been constantly filled with hepatitis cases. Since that date tests have been made with a fat diet in one department, a carbohydrate diet in another, and a protein diet in the third. Special diet personnel were employed in the kitchen purely for these tests. Diets were composed in such a way that all the departments received a basic diet consisting of 80 g. fats, 80 g. protein, and 320 g. carbohydrates. Those on a fat diet were given an extra 65 g. butter, partly in sauces, etc., with the food and partly on bread. The carbohydrate diet consisted of an extra 100 g. of ordinary sugar and 100 g. of sweet fruit juice. The sugar was usually given in lemon juice.

To obtain a diet rich in protein proved very difficult, as an increase to 200 g. protein in the form of meat, skimmed milk, etc., would have considerably altered the basic diet. In fact, a greater variation than 10% in the carbohydrate, fat, and protein in the basic diet was not permitted. An increase to 150 g. has, however, proved possible, and the remaining 50 g. has been given in the form of casein—25 g. cooked into the food, in porridge, rissoles, etc., and 25 g. taken as granulated casein orally. The calorie content in the different diets is thus about 3,000. Added vitamins were given equally in the three series—vitamin A and D pills, vitamin B complex as tablets, and vitamin K in relation to the prothrombin index.

Obviously, not all patients ate exactly 3,000 calories; some ate more, others less. So far as possible, however, an attempt was made to maintain the right proportions. In spite of the extreme nature of the diets the patients fared well on them, and in only two cases on the fat diet did light bowel disorders occur for a few days.

Once all the cases of uncertain diagnosis had been eliminated and all those excluded that had been discharged after July 1, when the differences in diet ceased, there remained in the protein series results of 128 cases, in the carbohydrate series 97, and in the fat series 86. (Cases discharged after July 1, but which had been on diet at least one month previously, were, however, included.) As we were overbooked, the next patient on the waiting-list was admitted as soon as a bed became free, and, as the fat and carbohydrate departments are more modern and have a larger number of small rooms, it was unavoidable that a certain number of elderly people were put in these, which made it impossible to arrange a non-selective test series. This occurred to an even greater degree when the material was divided into cases of epidemic and post-inoculation hepatitis, which was done by means of a special questionary. All cases in which inoculation (by blood tests, injections,



etc.) had not taken place within two to six months before sickness were classed as epidemic hepatitis. In order to obtain more comparable groups only the cases of epidemic hepatitis have been included. A rough classification of age and number of cases is shown in the Chart.

As will be seen, there is no statistical age difference between the various groups. A certain disparity in sexes occurs, but in these age groups this is not considered to be of any significance.

The patients have remained under treatment up to an icterus index of 10 or less (≷ 10), Meulengracht. In about 10% of cases, equally divided over the different series (10 out of 97, 6 out of 54, and 6 out of 56), it has been impossible to avoid earlier discharge, generally at an icterus index of 11 to 15, and never over 15. All tests were carried out at weekly intervals.

An idea of the severity of the hepatitis can be obtained from the maximum value of the icterus index, which was as follows in the different groups :

Prot.	..	42.5 ± 2.99.	Inc. on arrival in 11/97 (11.3%)
Carb.	..	40.7 ± 4.63.	„ „ „ „ 5/56 (8.9%)
Fats	..	42.0 ± 4.24.	„ „ „ „ 12/54 (22.2%)

That the icterus index is increasing to a higher degree in the cases on fat diet does not depend on their having been admitted to hospital at an earlier stage. If it is an effect of the diet, it does not seem to have influenced the duration of bilirubinaemia or to have had a negative effect on the course of the illness in other ways.

In order to judge the effect of the different diets, comparison must be made of duration of treatment, time up to Meulengracht ≷ 10 (isolated cases ≷ 15), maximum thymol value, and the thymol value at discharge; also the time until the urine becomes free of urobilin, bilirubin, and bile acids, and the increase of weight from the second week to discharge. The values obtained are shown in the accompanying Table.

Nowhere have our statistics shown any definite difference, nor even a tendency to such. Even if the children (up to 14 years) are excluded no statistical difference is obtained.

The result, so far as these series are concerned, seems therefore to be negative. Yet it is positive in so far as it shows that protein, carbohydrate, or fat diet, combined with a balanced basic diet, has no effect on the course of hepatitis.

Summary

In three parallel series of 97, 56, and 54 cases of acute epidemic hepatitis, diets of protein, carbohydrate, and fat, respectively, were given combined with a balanced basic diet. The calorie content was maintained at about 3,000. No statistical difference as regards duration of treatment or the time taken for the blood and urine tests to become normal has been found. A considerable measure of freedom can therefore be observed in the composition of the diet, as an excessive increase of protein, fat, or carbohydrate has no effect on the course of the illness.

		Protein Diet		Fat Diet		Carbohydrate Diet	
		No. of Cases	Mean	No. of Cases	Mean	No. of Cases	Mean
Age	All cases	97	22·4 ± 1·26 years	54	24·9 ± 2·15 years	56	23·9 ± 2·15 years
	Adults	67	28·7 ± 1·39 „	35	33·7 ± 2·08 „	34	34·2 ± 2·09 „
Duration of treatment	All cases	97	27·9 ± 1·26 days	54	28·9 ± 1·67 days	56	30·2 ± 2·25 days
	Adults	67	29·2 ± 1·61 „	35	30·9 ± 2·10 „	34	31·3 ± 3·40 „
Icterus index (Meulengracht) time to ≷ 10	All cases	97	3·0 ± 0·18 weeks	54	3·13 ± 0·23 weeks	56	3·30 ± 0·37 weeks
	Adults	67	3·36 ± 0·24 „	35	3·49 ± 0·28 „	34	3·50 ± 0·47 „
Icterus index maximum	All cases	97	42·5 ± 3·0	54	42·0 ± 4·2	56	40·7 ± 4·6
	Adults	67	49·4 ± 3·9	35	42·6 ± 6·0	34	46·1 ± 7·0
Thymol maximum	All cases	91	17·6 ± 0·82	44	16·2 ± 1·21	50	17·7 ± 1·15
	Adults	67	17·6 ± 0·99	35	16·0 ± 1·36	34	16·0 ± 1·37
Thymol at discharge	All cases	91	10·1 ± 0·53	44	8·9 ± 0·74	50	9·8 ± 0·88
	Adults	67	10·3 ± 0·67	35	9·1 ± 0·85	34	9·7 ± 1·14
Prothrombin index, lowest value after 2nd week	All cases	96	91·5 ± 1·38	54	93·6 ± 1·53	56	93·7 ± 1·56
	Adults	67	90·0 ± 1·76	35	92·9 ± 1·71	34	92·3 ± 1·82
Increase in weight from 2nd week until discharge	All cases	82	1·06 ± 0·17 kg.	41	1·37 ± 0·21 kg.	52	0·83 ± 0·18 kg
	Adults	58	1·07 ± 0·22 „	30	1·35 ± 0·27 „	31	0·88 ± 0·29 „
Urobilin (Schlesinger): Negative whole duration	All cases	97	50·5 ± 4·9%	54	46·3 ± 3·7%	56	42·9 ± 3·3%
	Adults	67	52·2 ± 4·1%	35	48·6 ± 3·0%	34	47·1 ± 2·9%
Positive at discharge	All cases	97	9·3 ± 2·9%	54	14·8 ± 2·6%	56	16·1 ± 2·8%
	Adults	67	9·0 ± 2·3%	35	20·0 ± 2·4%	34	14·7 ± 2·1%
Time until negative	All cases	39	3·0 ± 0·32 weeks	21	2·9 ± 0·29 weeks	23	2·48 ± 0·46 weeks
	Adults	26	3·46 ± 0·45 „	12	3·25 ± 0·42 „	13	2·77 ± 0·71 „
Bile acids (Hay): Negative whole duration	All cases	97	29·9 ± 4·5%	53	24·5 ± 3·1%	56	16·1 ± 2·8%
	Adults	67	10·9 ± 3·3%	35	20·0 ± 2·4%	34	One case
Positive at discharge	All cases	97	3·1 ± 1·7%	53	11·3 ± 2·3%	56	17·9 ± 2·9%
	Adults	67	1·5%	35	14·3 ± 2·1%	34	23·5 ± 2·6%
Time until negative	All cases	65	1·98 ± 0·13 weeks	34	2·26 ± 0·20 weeks	37	2·0 ± 0·25 weeks
	Adults	52	2·14 ± 0·15 „	23	2·57 ± 0·34 „	25	2·24 ± 0·35 „
Bilirubin (Hammarsten): Negative whole duration	All cases	97	54·6 ± 4·9%	53	56·6 ± 3·6%	56	56·1 ± 3·5%
	Adults	67	49·3 ± 4·1%	35	48·6 ± 3·0%	34	58·8 ± 2·9%
Positive at discharge	All cases	97	0	53	0	56	3 cases—all adults
Time until negative	All cases	44	1·79 ± 0·18 weeks	23	1·78 ± 0·22 weeks	16	1·37 ± 0·22 weeks
	Adults	34	1·78 ± 0·22 „	18	1·89 ± 0·26 „	11	1·54 ± 0·25 „

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METHIONINE IN THE TREATMENT OF ACUTE HEPATITIS

BY

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Experimental tests made on animals during the past ten years have shown the deleterious effect on the liver and its functions caused by insufficiency of protein in the diet. It has further been shown that the cause is a qualitative, not a quantitative, lack of protein. Liver necrosis and cirrhosis occurring in animals can therefore be prevented by giving sulphur-containing amino-acids, of which the most important is methionine. Damage caused by liver poisoning can also be prevented with methionine.

Even if the actual mechanism by which methionine protects the liver is unknown, it is natural to attempt to use it therapeutically in cases of acute hepatitis; for the damage to liver cells caused by virus may possibly be reduced, the processes of healing be speeded up, or both. The experience gaincd from such experiments has so far been insufficient and the results are contradictory. Wilson, Pollock, and Harris (1945) treated 50 patients with 5 g. of methionine daily until the urine had been free from bile pigments for five days. Comparing these cases with 50 simultaneous control cases, they found "no significant effect on the severity or duration of the disease." Nor did Higgins *et al.* (1945) in their tests on 18 patients, with an equal number of control cases, find any effect on the course of the disease or the duration of bilirubinaemia or bilirubinuria.

Beattie and Marshall (1944), on the other hand, briefly state that good results have been obtained in 450 cases of hepatitis and arsphenamine icterus, especially in cases of severe illness. They considered the effect "so striking as to leave no doubt." Peters *et al.* (1944) found that methionine had a definite effect (cited by Iversen, 1946). Barclay *et al.* (1945) claim dramatic results from the use of methionine intravenously (10 g. daily) in two cases. Eddy (1945) records beneficial results from methionine treatment of toxic hepatitis caused by trinitrotoluene and carbon tetrachloride.

Morrison (1947) obtained a considerable improvement when treating liver cirrhosis with choline and methionine; and Beams and Endicott (1947) used methionine alone with beneficial effects, shown both by biopsy of the liver and by tests of liver functions.

Present Investigation

The investigation began in October, 1947, and continued until the end of December, 1948. Every alternate case of acute hepatitis, with the exception of patients under 10 years of age, was put on methionine treatment (5 g. daily for 10 days), the other case serving as a control and receiving dummy tablets. Each series consisted finally of 125 cases—described as the C. (control) and M. (methionine) series. The average age in both was almost exactly identical (32.7 ± 1.1 and 32.8 ± 1.2 years). The diet was the same for all patients (about 90 g. protein, 90 g. fat, and 400 g. carbohydrate—2,850 calories).

No attempt was made to divide the material into epidemic and inoculation hepatitis. The former is the more common in our hospital. (An analysis of the hospital material by Gertzén and Ström in 1948 showed that at least 62% of the cases, and probably many more, were in the epidemic group.)

The material was tested once a week for the icterus index (Meulengracht), thymol and prothrombin content of the blood, bilirubin (after Hammarsten), bile acids (Hay), and urobilin (Schlesinger) in the urine.

With regard to the colour index of the blood it would have been more correct to follow the return of the index to the value of Meulengracht 10, but, as some patients had for various reasons left the hospital earlier, I took a value of 15 or less ($\leqslant$ 15). Only three patients out of 250 were discharged with a higher value, and these are not included in the calculations. This fact is of no importance from the point of view of the material.

A calculation was made of the highest icterus index and the time in weeks for a return to $\leqslant$ 15. In the same way the highest thymol reaction value was calculated, also the value at discharge, as the thymol content usually remains high longer than the bilirubinaemia and it has therefore been impossible to indicate when normal is reached. In the case of prothrombin the lowest value was calculated on an index obtained from the second week in hospital. It should be noted that all patients received vitamin K daily according to schedule. For bile pigments, bile acids, and urobilin in the urine I have calculated the time in weeks until negative tests were obtained.

The figures of different blood reactions in Table I show that the M. series had fewer cases in which bilirubinaemia increased after admission to hospital and a slightly smaller

TABLE I

Reaction	C. Series	M. Series
Meulengracht:		
Highest value	46·5±2·9	44·3±2·9
Cases increasing after admission	29	20
Time in weeks for decrease to $\leqslant$ 15	3·3±0·19	2·9±0·17
Thymol:		
Highest value	18·5±0·9	20·0±1·1
At discharge	11·5±0·6	11·6±0·6
Prothrombin:		
Lowest value	92·5±1·4	94·5±1·2

increase of bilirubinaemia than the C. series. In the C. series, also, the time was longer before the icterus index decreased to 15 or less. The thymol reaction shows slightly higher values in the M. series, but at discharge they were the same in both series. The prothrombin index has lower values in the C. than in the M. series. However, statistically proved differences were not obtained. Data concerning the secretion of bile products and their derivatives in the urine are shown in Table II. (Here I would point out that, because so many cases showed no bilirubin or urobilin in the urine, tests were made only once a week.) It will be seen that in the M. series more cases were free from bile pigments, that the duration of bilirubinuria was also somewhat shorter, and that the number of cases positive